# Easy Access to Phosphonothioates

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**Abstract:** A new and particularly mild method for the formation of phosphorus–sulfur bonds has been achieved through base-catalyzed addition of thiocyanate to the corresponding H-phosphine oxide, phosphinate, or phosphonate. This reaction procedure offers many advantages: the use as starting material of a stable and not oxygen-sensitive phosphorus(v) species, particularly mild and nonaqueous reaction conditions and workup (a pivotal point for these sensitive phosphonothioates), and, through optimized access to thiocyanates, a wider scope of substrates. This method has been applied to achieve the synthesis of substrate analogues for the study of antibody-catalyzed hydrolysis of acetylcholinesterase inhibitor PhX (**11**).

**Keywords:** phosphorothioates · phosphorylation · thiocyanates · toxicology

## Introduction

Phosphonothioates and thiophosphonates are increasingly widely used in biological applications, mainly as enzymatically stable phosphate analogues for pest control,[1] but also as non-hydrolysable ribonucleotide mimics for use in chemotherapy.[1a–b, 2] Phosphonothioate VX [*S*-2-(diisopropylamino)ethyl *O*-ethyl methylphosphonothioate, also known as A4] has, for instance, been described as the most powerful acetylcholinesterase inhibitor.[3] In the course of our studies on catalytic antibodies, aimed at the neutralization of this highly toxic nerve agent,[4] we needed to synthesize a number of less toxic phenylphosphonothioate analogues of these methylphosphonothioates. Because of the presence of a highly basic nitrogen-bearing side chain, classical methods of synthesis of the phosphorus–sulfur bond failed.[5] We had to develop a new and mild method for the formation of this fragile P–S bond, without any acidic, basic, or even aqueous workup.

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## Results and Discussion

Among the means allowing efficient access to phosphonothioates, the Michaelis–Arbuzov-like addition of sulfenyl halides,[6] thiosuccinimides/phthalimides,[7] or disulfides[8] to phosphites offers an easy workup of the required kind. However, phosphites are highly oxygen-sensitive species, and the reaction conditions required for the formation either of sulfenyl chloride or of thiosuccinimides proved to be incompatible with the nitrogen-bearing side chain, and—in the few cases in which their synthesis has been achieved—many by-products were formed together with the phosphonothioate.[9] As far as nonactivated disulfides are concerned, they display too low a reactivity, high reaction temperatures are required, and one half of the side chain has to be discarded in the process. Unsymmetrical activated (through 2-nitro- and 2,4-dinitrophenylsulfenyl) disulfides also provide reactive substrates for Michaelis–Arbuzov and Michaelis–Arbuzov-like addition to phosphites,[10] but their synthesis is incompatible with many functional groups. We therefore turned to thiocyanates as pseudo-halogens for the Michaelis–Arbuzov-like reaction. Only one such example has been described,[11] and its requirement for a high reaction temperature proved to be incompatible with the thermally unstable thiocyanate moieties. As an illustration, *O*,*O*-diethyl phenylphosphonite was heated with *N*,*N*-diisopropylaminoethyl thiocyanate (**3a**) (see Scheme 1; prepared from the corresponding alcohol and lead thiocyanate as previously described[12]). Whatever the reaction conditions we used, no trace of the corresponding phosphonothioate was detected.

In order to develop a practical synthetic scheme for diversely substituted phosphonothioates, two issues had to

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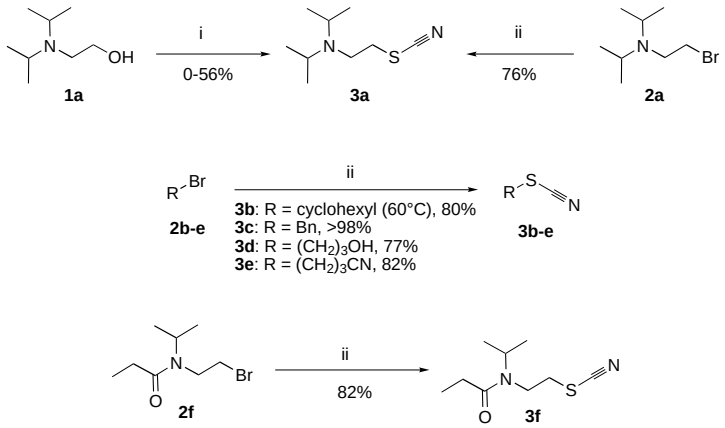
be addressed: 1) with the classical thiocyanation methods we were using we were faced with both low yields and poor reproducibility, and so accessibility to a wide array of sulfur-bearing side chains required optimized access to substituted alkyl thiocyanates, and 2) alkyl thiocyanates being thermally unstable, and the targeted phosphonothioates particularly sensitive, mild phosphorus–sulfur bond formation under nonthermal conditions had to be achieved.




Scheme 1. Formation of thiocyanates: i) $Pb(SCN)_2$, $Br_2$ then $PPh_3$, 0 °C, $CH_3CN$; ii) $Me_3Si$-N=C=S, $n$Bu$_4$NF, THF.

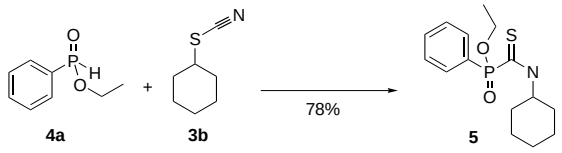
**Optimized access to alkyl thiocyanates**: Alkyl thiocyanates are one of the most important synthetic intermediates for the preparation of sulfur-containing organic compounds. Not only have natural products containing the thiocyanate group attracted attention,[13] but this functional group can also be used as a masked mercapto group or a precursor for sulfur-containing heterocycle compounds. Yet the low nucleophilicity of the $NCS^-$ ion, compared with that of simple thiols, requires relatively harsh reaction conditions. For introduction of the thiocyanate group into an organic molecule, the use of metal thiocyanates (usually K-SCN, Na-SCN, or $Zn(SCN)_2$ formed in situ) with organic halides or sulfonates has been generalized.[14] However, the thiocyanate group is poorly stable when heated or subjected to acidic conditions. Simple chromatography on silica gel or prolonged heating over 70 °C can cause intramolecular rearrangement to the thermodynamically favored isothiocyanate isomer (this rearrangement occurs preferentially with primary thiocyanates, and so heating or use of dissociative solvents such as HMPA or DMF should be avoided for such fragile compounds).[15] Thiocyanates can also be obtained from alcohols,[12] silyl ethers,[16] or amines[17] by use of the electrophilic phosphorane $Ph_3P(SCN)_2$, produced in situ. However, the results are unreliable and not reproducible because of the low thermal stability of the required intermediate $(SCN)_2$, and—once again—various quantities of rearranged isothiocyanate by-products. This substitution has also been performed on alkyl halides with trimethylsilyl isothiocyanate, but only when activated with a stoichiometric amount of a strong Lewis acid such as $TiCl_4$[18] or when the reaction is performed on activated benzylic compounds with HMPA as solvent.[19] In any case, variable quantities of contaminating isothiocyanates were also formed. We had previously found that when trimethylsilyl isothiocyanate was treated with stoichiometric amounts of tetrabutylammonium fluoride, the tetrabutylammonium thiocyanate salt formed in situ afforded an improved route to alkyl thiocyanate through nucleophilic substitution of alkyl halide.[20] This reaction offered a particularly easy workup, gave superior and reproducible yields, and could be performed at room temperature, preventing the formation of rearranged isothiocyanate by-products. For primary alkyl bromides, reaction was complete after overnight (or one hour for highly reactive benzyl bromide) standing at room temperature. For a secondary alkyl bromide (**2b**), three days heating in THF at 60 °C with an excess (1.5 equiv) of $n$Bu$_4$N-SCN was required. Careful temperature monitoring was crucial. Under these reaction conditions, no trace of isothiocyanate was detected by GC/MS. For thiocyanates **3b**–**f**, successive precipitation of the resulting tetrabutylammonium salts with diethyl ether and pentane gave thiocyanates of $>98\,\%$ purity as determined by GC/MS. For **3a**, flash chromatography had to be undertaken. The main results are summarized in Scheme 1.

Notably, such a method for the formation of thiocyanates gave high yields of functionalized thiocyanates **3a**, **3d**, and **3f**, whereas formation of the corresponding sulfenyl chlorides and thiosuccinimides either failed or gave poor yields together with troublesome purification procedures.

**Phosphorothioate formation**: For phosphorus–sulfur bond formation, we decided to use H-phosphonates as air-stable phosphorus starting materials. Two strategies were then feasible: either the Michaelis–Arbuzov-like condensation on reactive *O*-trimethylsilyl phosphonite, formed in situ,[10] or

**Abstract in French:** *Dans cet article, nous décrivons une nouvelle méthode, particulièrement douce, de formation d'une liaison phosphore soufre. Elle consiste en l'addition, en présence d'une quantité catalytique de base, d'un thiocyanate sur un hydrogéno oxyde de phosphine, phosphinate ou phosphonate. Cette procédure offre plusieurs avantages: les produits de départs sont des espèces du phosphore(v) stables et peu sensibles à l'oxygène; le traitement se fait dans des conditions douces et non aqueuse, un point crucial pour les phosphonothioates fragiles formés; enfin, grâce à un accès optimisé à divers phosphonothioates, un plus large panel de produits de départ est accessible. Cette méthode a été appliquée à la synthèse d'analogues de substrats pour l'étude de la catalyse abzymatique de l'hydrolyse d'inhibiteurs de l'acétylcholine estérase comme le PhX (**11**).*

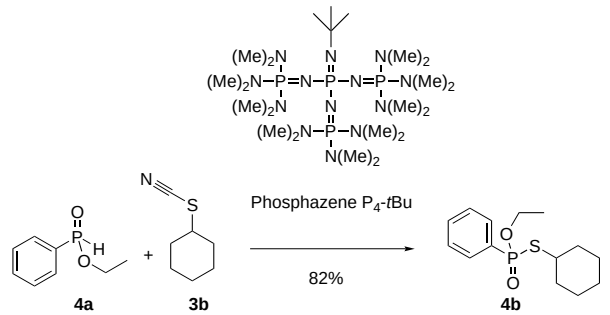
nucleophilic addition to activated sulfur in the thiocyanate derivatives. The Pudovik (or Abramov – Pudovik)[21] reaction is well known for the construction of P–C bonds. Namely, $\alpha$-hydroxyphosphonate is formed through nucleophilic addition of anions of phosphinic acids to electrophiles such as aldehydes or ketones. As in the more reactive sulfenyl halide or thiosuccinimide/phthalimide, the sulfur atom in the thiocyanate group is also likely to be the target of nucleophilic addition. Conventional Pudovik conditions (heating under base-catalyzed conditions, typically with alkoxides of tertiary amines) or milder procedures (silyl-Abramov reaction with in situ preparation of silylphospho(i)nite by heating of H-phospho(i)nates under reflux with neat hexamethyldisilazane)[21c] failed due to the thermal instability of alkyl thiocyanate.[15] This side reaction is shown in Scheme 2, for an initial attempt at thermally-induced Pudovik addition of *O*-ethyl phenylphosphinate (**4a**) to cyclohexyl thiocyanate (**3b**) with a stoichiometric amount of base. Almost complete isomerization of cyclohexyl thiocyanate to cyclohexyl isothiocyanate occurred, yielding 78% phosphinate **5** and only trace amounts of the targeted phosphonothioate.




Scheme 2. Thermal Pudovik-like addition of cyclohexyl thiocyanate (*i*Pr$_2$NEt, DMF, 110 °C).

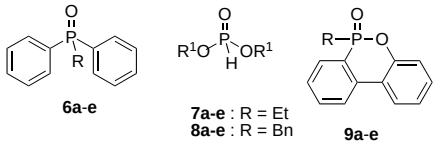
In sharp contrast to this result, we found that when the reaction was performed at room temperature, with toluene as solvent and either a stoichiometric amount of diisopropylethylamine or a catalytic amount of a stronger, hindered, nonnucleophilic base such as phosphazene P$_4$-*t*Bu[22] (1%) or DBU (5%), the Pudovik-like reaction took place readily at room temperature. As summarized in Scheme 3 and Table 1, high yields of phospho-, phosphono-, or phosphinothioates could be isolated after simple filtration on a pad of silica gel or flash chromatography of the crude reaction mixture.

The best yields and shorter reaction times were observed with the highly reactive benzyl thiocyanate (**3c**). Unactivated primary (**3e**) and secondary (**3b**) alkyl thiocyanates gave




Scheme 3. Room temperature Pudovik-like addition of ethyl phenylphosphonate to cyclohexyl thiocyanate (phosphazene P$_4$-*t*Bu (1%), toluene, 3 h, 25 °C).

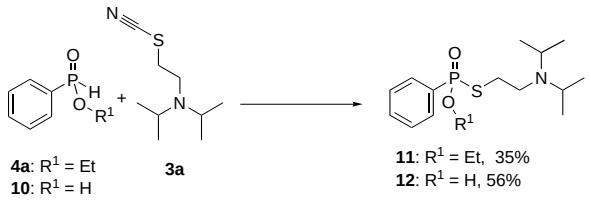
Table 1. Nucleophilic addition of H-phosphonates (**7a**, **8a**), phosphinates (**4a**, **9a**), or phosphine oxide (**6a**) to alkylthiocyanates, catalyzed by phosphazene P$_4$-*t*Bu.[a]




| Phosphorus derivative | R-SCN | Product (Yield [%]) |
|---|---|---|
| **4a** | **3b** | **4b** (82) |
| | **3c** | **4c** (93)[b] |
| | **3d** | **4d** (50) |
| | **3e** | **4e** (94) |
| **6a** | **3b** | **6b** (86) |
| | **3c** | **6c** (88)[b] |
| | **3d** | **6d** (34) |
| | **3e** | **6e** (83) |
| **7a** | **3b** | **7b** (79) |
| | **3c** | **7c** (86)[b] |
| | **3d** | **7d** (68) |
| | **3e** | **7e** (81) |
| **8a** | **3b** | **8b** (82) |
| | **3c** | **8c** (90)[b] |
| | **3d** | **8d** (54)[c] |
| **9a** | **3b** | **9b** (85) |
| | **3c** | **9c** (87)[b] |
| | **3e** | **9e** (92)[c] |

The reaction was performed in toluene (0.25 M), with 1% hindered base as catalyst, for 3 h at room temperature. The yield of isolated product is indicated. [b] Reaction time: 1.5 h. [c] Reaction time: 18 h.

good yields, whereas free alcohol **3d** gave lower but still acceptable yields. This reaction procedure was then extended to the less toxic phenylphosphonothioate analogues of methylphosphonothioate VX (Scheme 4). As thiocyanate **3a** already bears a highly basic moiety, use of an additional base




Scheme 4. Synthesis of VX analogues (THF, 70 °C, 24 h or neat, 25 °C, 10 d).

was not necessary. Mild heating (70 °C, THF) of a stoichiometric mixture of thiocyanates with *O*-ethyl phenylphosphinate (**4a**) for 24 hours or stirring at room temperature under a gentle nitrogen flow for 10 days gave almost quantitative yields of the corresponding phosphonothioate, as estimated by $^{31}$P NMR and GC/MS analysis of the crude reaction mixture. Yet purification of those highly sensitive products was particularly tricky. In our hands, the best purification procedure proved to be semipreparative HPLC with a Zorbax SB-CN column and a hexane/methyl *tert*-butyl ether (60:40) mixture as mobile phase.

As an illustration of the role of the basic nitrogen atom in the thiocyanate, no addition was observed when thiocyanate **3f**, bearing an amide moiety instead of the amine moiety

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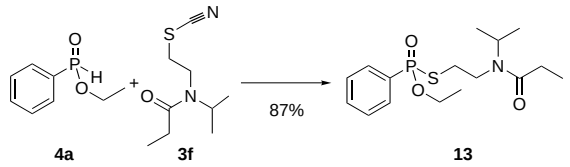
(R = C(O)Et), was heated with *O*-ethyl phenylphosphinate (**4a**). Heating only promoted degradation of the thiocyanate moiety. On the other hand, treatment of this thiocyanate with 1% phosphazene $P_4$-*t*Bu in toluene at room temperature provided, after 3 hours, an 87% yield of phosphonothioate **13** (Scheme 5) (to be compared with 26% after 24 hours heating at 70 °C with 1 equiv triethylamine).




Scheme 5. Synthesis of phosphonothioate **13** (Phosphazene $P_4$-*t*Bu (1%), toluene).

During the hydroxide-promoted hydrolysis of methylphosphonothioate VX, both side chains can be cleaved, yielding nontoxic *O*-ethyl methylphosphonic acid (88%), together with the still toxic *S*-2-(diisopropylamino)ethyl methylphosphonothioic acid (12%).[23] The same hydrolysis profile was observed with phenylphosphonothioate (**11**). In our efforts aimed at the degradation of these neurotoxic warfare agents, the amount of the still toxic P–O bond-cleavage by-products has to be carefully monitored. Conventional methods for the formation of these phosphonothioic acids in good yields failed. Only the use of our Pudovik-like condensation of phenylphosphinic acid **10** on the two alkyl thiocyanates gave satisfactory yields after 10 days at room temperature (Scheme 4).

## Conclusion

In conclusion, we have shown that addition of H-phosphi(o)nate to thiocyanate under catalysis by hindered, nonnucleophilic bases appears to be a mild alternative route for the formation of the P–S bond. This type of reaction requires two parameters to be carefully balanced: reactivity at the sulfur atom and accessibility to this activated moiety. In our hands, thiocyanates displayed such features and proved compatible with a wider array of functional groups than previously described sulfur activated species.

## Experimental Section

**General remarks**: Reagents were purchased from Aldrich. All solvents were distilled before use, and reactions were performed under $N_2$ atmosphere. All chromatography (flash) was performed with Merck Silica gel 60 (0.02–0.04 mm). TLC was performed with fluorescent Merck F254 glass plates. NMR spectra were recorded on a Bruker AC 300 (300.15 MHz for $^1$H, 75.4 MHz for $^{13}$C, and 121.5 MHz for $^{31}$P) in $CDCl_3$ unless stated otherwise. Chemical shifts ($\delta$) are given in ppm and the coupling constants ($J$) are expressed in Hertz. MS were obtained with a Finnigan–Mat 4600 quadrupole system (chemical ionization with $NH_3$). Flash column chromatography was performed on Merck silica gel (60 Å, 230–400 mesh). Elemental analyses were recorded at the Institut de Chimie des Substances Naturelles, Gif sur Yvette.

**General procedure for thiocyanation of alkyl bromide**: Trimethylsilyl isothiocyanate (140 μL, 1.1 mmol) was added at room temperature to a solution of bromide (1.0 mmol) in dry THF (10 mL). Tetrabutylammonium fluoride (1.1 mL of a 1.0 M solution in THF) was then added dropwise. The reaction course was monitored either by TLC or by GC/MS. Once the reaction was complete, THF was evaporated, and the reaction mixture was triturated with pentane. Simple filtration of tetrabutylammonium salts yielded thiocyanate, the purity of which was checked by GC/MS. When needed, further flash chromatography on silica gel was performed.

***N,N*-Diisopropyl-(2-thiocyanatoethyl)-amine (3a) from 2-diisopropylaminoethanol**: Bromine (150 μL, 2.86 mmol) dissolved in acetonitrile (10 mL) was added dropwise to a suspension of lead thiocyanate (1.0 g, 3.12 mmol) in acetonitrile (50 mL), cooled to 0 °C. Once the addition was complete, the lead bromide was decanted, and the supernatant was added dropwise to a cooled (−40 °C) solution of triphenylphosphine (750 mg, 2.9 mmol) dissolved in acetonitrile (15 mL). After 30 min at −40 °C, 2-diisopropylaminoethanol (460 μL, 2.6 mmol) dissolved in acetonitrile (10 mL) was added dropwise, and the reaction mixture was kept for 2 h at −40 °C, and then allowed to reach room temperature overnight. Solvents were then evaporated in vacuo, and the crude reaction mixture was chromatographed on silica gel (hexane/ethyl acetate 95:5) to yield thiocyanate **3a** (272 mg, 56%) as a pale yellow oil.

***N,N*-Diisopropyl-(2-thiocyanatoethyl)-amine (3a) from (2-bromoethyl)diisopropylamine**: The thiocyanation procedure was undertaken on the bromide (1.12 g, 3.92 mmol), yielding the thiocyanate (540 mg, 76%) after flash chromatography (pentane/ethyl acetate 80:20). $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 3.11$ (t, $^3J(H,H) = 7$ Hz, 2H), 2.97 (hept, $^3J(H,H) = 6.5$ Hz, 2H), 2.80 (t, $^3J(H,H) = 7$ Hz, 2H), 0.99 (d, $^3J(H,H) = 6.5$ Hz, 12H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 114.0$ (SCN), 48.1 (2C), 43.6, 35.9, 20.8 (4C); MS (I.C./$NH_3$): $m/z$ (%): 187 (100) $[M+H]^+$; IR (neat): $\tilde{\nu} = 2968$, 2152 (SCN), 1464, 1388, 1366, 1289, 1205, 1161 cm$^{-1}$; elemental analysis calcd (%) for $C_9H_{18}N_2S$ (188.2): C 58.02, H 9.74, N 15.03; found C 58.41, H 9.69, N 14.51.

**Thiocyanatocyclohexane (3b)**: white powder; m.p. 38–39 °C (decomp); $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 3.7$ (tt, $^3J(H,H) = 4.0$, 11.0 Hz, 1H), 2.04 (dd, $^3J(H,H) = 3.0$, 13.0 Hz, 2H), 1.75 (dt, $^3J(H,H) = 9.0$, 4.0 Hz, 2H), 1.60–1.10 (m, 6H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 111.05$ (SCN), 47.4, 33.2 (2C), 25.4 (2C), 24.4; IR (KBr): $\tilde{\nu} = 2938$, 2857, 2151 (SCN), 1450, 1343, 1263, 1206, 994, 889, 716 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 159 $[M+NH_4]^+$ (100), 176 $[M+N_2H_7]^+$ (70).

**Benzyl thiocyanate (3c)**: This compound was identical to the commercially available product. White powder; m.p. 41–42 °C (lit: 41.5–43 °C); $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.35$ (m, 5H), 4.09 (s, 2H); IR (KBr): $\tilde{\nu} = 3033$, 2992, 2145 (SCN), 1491, 1453, 1425, 1243 cm$^{-1}$; elemental analysis calcd (%) for $C_8H_7NS$: C 64.40, H 4.73, N 9.35; found C 64.37, H 4.69, N 9.44.

**3-Thiocyanato-propan-1-ol (3d)**: Colorless oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta =$ 3.73 (t, $^3J(H,H) = 6.0$ Hz, 2H), 3.06 (t, $^3J(H,H) = 6.0$ Hz, 2H), 2.53 (br s, 1H, OH), 2.01 (quint, $^3J(H,H) = 6.0$ Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 112.4$ (SCN), 59.3, 31.7, 30.15; IR (neat): $\tilde{\nu} =$ 3421, 2947, 2883, 2155 (SCN), 1643, 1427, 1051, 915 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 135 $[M+NH_4]^+$.

**4-Thiocyanatobutyronitrile (3e)**: Colorless oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 3.08$ (t, $^3J(H,H) = 7.0$ Hz, 2H), 2.60 (t, $^3J(H,H) = 7.0$ Hz, 2H), 2.21 (quint, $^3J(H,H) = 7.0$ Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 118.1$ (CN), 111.2 (SCN), 32.1, 25.6, 15.7; IR (neat): $\tilde{\nu} = 2939$, 2875, 2249 (CN), 2155 (SCN), 1448, 1425, 1285, 1265 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 144 $[M+NH_4]^+$ (100).

***N*-Isopropyl-*N*-(2-thiocyanatoethyl)-propionamide (3f)**: Trimethylsilyl isothiocyanate (140 μL, 1.1 mmol) was added at room temperature to a solution of bromide **2f** (222 mg, 1.0 mmol) in dry THF (10 mL). Tetrabutylammonium fluoride (1.1 mL of a 1.0 M solution in THF) was then added dropwise. The reaction course was monitored by TLC, and after the mixture had stirred for 16 hours, THF was evaporated, and the reaction mixture was triturated with pentane. Filtration yielded thiocyanate **3f** as a yellow oil (174 mg, 87% yield, 95% pure as estimated by GC/MS), which could either be used directly or be subjected to flash chromatography on silica gel ($CH_2Cl_2$/MeOH 98:2) to yield a pale yellow oil (124 mg, 62%). $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 4.10$ (quint, $^3J(H,H) = 6.5$ Hz, 1H), 3.55 (t, $^3J(H,H) = 5$ Hz, 2H), 3.15 (t, $^3J(H,H) = 5$ Hz, 2H), 2.39 (q, $^3J(H,H) = 7.5$ Hz, 2H), 1.25 (d, $^3J(H,H) = 6.5$ Hz, 6H), 1.15 (t, $^3J(H,H) =$

7.5 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 174.1$, 112.2 (SCN), 53.5; 48.4, 41.2, 31.6, 26.9, 21.3, 9.4; IR (neat): $\tilde{\nu} = 2979$, 2154 (SCN), 1742, 1639 (C=O), 1461, 1422, 1158, 1071 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 201 $[M+H]^+$ (40), 218 $[M+NH_4]^+$ (100).

**[(Cyclohexylamino)thioxomethyl]-phenylphosphinic *O*-ethyl ester (5)**: A mixture of thiocyanato cyclohexane **3b** (141 mg, 1 mmol), diisopropylethylamine (174 µL, 1 mmol), and ethyl phenylphosphinate **4a** (151 µL, 1 mmol) in dry DMF (10 mL) was heated under reflux for 4 h. After the mixture had cooled, DMF and amine were evaporated under vacuum, and the crude reaction mixture was chromatographed ($CH_2Cl_2$/acetone 9:1) to yield thioamide **5** (243 mg, 78%) as a pale yellow powder. M.p. 109–109.5 °C; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 9.45$ (br t, 1H; NH), 7.98 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 4.39 (m, 1H), 4.15 (m, 2H), 2.10 (m, 1H), 1.98 (m, 1H), 1.80–1.60 (m, 4H), 1.38 (t, $^3J$(H,H) = 7.5 Hz, 3H), 1.35 (m, 2H), 1.23 (m, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 193.8$ (d, $^1J$(P,C) = 119 Hz), 133.2, 133.1 (d, $^2J$(P,C) = 12 Hz, 2C) 128.3 (d, $^3J$(P,C) = 12 Hz, 2C), 127.55 (d, $^1J$(P,C) = 144 Hz), 62.7 (d, $^2J$(P,C) = 5 Hz), 54.2 (d, $^3J$(P,C) = 5 Hz), 31.1, 31.0, 25.4, 24.9 (2C), 16.4 (d, $^4J$(P,C) = 5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.59$; MS (I.C./$NH_3$): $m/z$ (%): 312 $[M+H]^+$ (80), 329 $[M+NH_4]^+$ (100).

**General procedure for phosphonothioate formation**: Phosphazene $P_4$-*t*Bu (1.0 M in *n*-hexanes, 0.025 mL, as supplied by Fluka) was added to a mixture of phosphinate (2.5 mmol, as supplied by Aldrich) and alkyl thiocyanate (2.5 mmol, prepared as previously described) in toluene (10 mL).

**Caution**: In order to remove produced hydrogen cyanide, a gentle nitrogen flow to a bubbling bottle containing 1.0 M aqueous sodium hydroxide solution has to be used, and the pH of the solution was regularly checked and maintained (>12). Once TLC or GC/MC indicated the complete consumption of the starting products, the solvents were evaporated, and the crude reaction mixture was directly chromatographed on silica gel ($CH_2Cl_2$/acetone 8:2).

**Phenylphosphonothioic acid *S*-cyclohexyl ester *O*-ethyl ester (4b)**: Colorless oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.90-7.80$ (m, 2H), 7.61–7.55 (m, 1H), 7.52–7.45 (m, 2H), 4.21 (m, 2H), 3.15 (q of t, $^3J$(P,H) = $^3J$($H_{ax}$,$H_{ax}$) = 11 Hz, $^3J$($H_{ax}$,$H_{eq}$) = 4 Hz, 1H), 1.90 (m, 1H), 1.80 (m, 1H), 1.70–1.55 (m, 2H), 1.50–1.10 (m, 5H), 1.30 (t, $^3J$(H,H) = 7.0 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 132.4$ (d, $^1J$(P,C) = 105 Hz), 132.4, 131.1 (d, $^2J$(P,C) = 10 Hz, 2C), 128.5 (d, $^3J$(P,C) = 11 Hz, 2C), 62.1 (d, $^2J$(P,C) = 7 Hz), 45.1, 35.5 (d, $J$(P,C) = 5 Hz), 35.34 (d, $^3J$(P,C) = 5 Hz), 25.9 (2C, $^4J$(P,C) = 5 Hz), 25.34, 16.4 (d, $^4J$(P,C) = 7.5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 44.70$; IR (neat): $\tilde{\nu} = 2982$, 2931, 2854, 1441, 1231, 1118, 1024, 952 cm$^{-1}$; MS (ESI-TOF): $m/z$ (%): 285 $[M+H]^+$; elemental analysis calcd (%) for $C_{14}H_{21}O_2PS$: C 59.13, H 7.44; found C 58.85; H 7.24.

**Phenylphosphonothioic *S*-benzyl ester *O*-ethyl ester (4c)**: Colorless oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.90-7.80$ (m, 2H), 7.61–7.55 (m, 1H), 7.52–7.45 (m, 2H), 7.22 (m, 5H), 4.35–4.09 (m, 2H), 4.05–3.90 (m, 2H), 1.30 (t, $^3J$(H,H) = 7.0 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 137.1$ (d, $^3J$(P,C) = 5 Hz), 132.4, 132.65 (d, $^1J$(P,C) = 105 Hz), 131.05 (d, $^2J$(P,C) = 10 Hz, 2C), 128.75 (2C), 128.45 (2C), 128.4 (d, $^3J$(P,C) = 11 Hz, 2C), 127.3, 62.1 (d, $^2J$(P,C) = 7 Hz), 34.4, 16.2 (d, $^4J$(P,C) = 5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 44.20$; IR (neat): $\tilde{\nu} = 3061$, 3030, 2982, 2929, 1602, 1590, 1495, 1454, 1438, 1391, 1227, 1119, 1022, 954 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 310 $[M+H]^+$.

**Phenylphosphonothioic *O*-ethyl ester *S*-(3-hydroxypropyl) ester (4d)**: Colorless oil; $^1$H NMR (300.15 MHz, $CDCl_3$), $\delta = 7.95-7.80$ (m, 2H), 7.61–7.45 (m, 3H), 4.26 (m, 2H), 3.86–3.79 (m, 1H), 3.72–3.65 (m, 1H), 3.48 (broad s, OH), 3.08–2.87 (m, 2H), 1.92–1.72 (m, 2H), 1.40 (t, $^3J$(H,H) = 7.0 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 132.7$, 132.4 (d, $^1J$(P,C) = 120 Hz), 131.15 (d, $^2J$(P,C) = 12.5 Hz, 2C), 128.7 (d, $^3J$(P,C) = 15 Hz, 2C), 62.7 (d, $^2J$(P,C) = 7.5 Hz), 58.9, 33.4, 26.5, 16.4 (d, $^4J$(P,C) = 8.5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 47.11$; IR (neat): $\tilde{\nu} = 3466$ (broad), 2930, 1439, 1214, 1119, 1021, 956 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 261 $[M+H]^+$ (85), 278 $[M+NH_4]^+$ (100).

**Phenylphosphonothioic acid *S*-(3-cyanopropyl) ester *O*-ethyl ester (4e)**: Pale yellow oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.92-7.80$ (m, 2H), 7.63–7.45 (m, 3H), 4.26 (m, 2H), 2.99–2.79 (m, 2H), 2.43 (td, $^3J$(H,H) = 7.0 Hz, $^5J$(P,H) = 3.0 Hz, 2H), 1.98 (quint. d, $^3J$(H,H) = 7.0 Hz, $^4J$(P,H) = 3.0 Hz, 2H) 1.41 (t, $^3J$(H,H) = 7.0 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 132.9$, 132.5 (d, $^1J$(P,C) = 115 Hz), 131.2 (d, $^2J$(P,C) = 10 Hz, 2C), 128.8 (d, $^3J$(P,C) = 14 Hz, 2C), 118.7, 62.7 (d, $^2J$(P,C) = 7.5 Hz), 28.8, 26.6, 16.4 (d, $^4J$(P,C) = 7.5 Hz), 15.9; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 44.20$; IR (neat): $\tilde{\nu} = 2984$, 2926, 2247 (CN), 1439, 1227, 1119, 1021, 956 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 287 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{11}H_{17}O_3PS$: C 50.76, H 6.58; found C 50.65, H 6.71.

**Diphenylphosphinothioic *S*-cyclohexyl ester (6b)**: Pale orange crystals; m.p. 81–82 °C; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.90-7.80$ (m, 4H), 7.52–7.35 (m, 6H), 3.27 (q of t, 1H, $^2J$(H,P) = $^3J$($H_{ax}$,$H_{ax}$) = 10.5 Hz, $^3J$($H_{ax}$,$H_{eq}$) = 3.5 Hz), 1.96–1.81 (m, 2H), 1.69–1.57 (m, 2H), 1.55–1.40 (m, 3H), 1.33–1.15 (m, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 134.2$ (d, $^1J$(P,C) = 105 Hz, 2C), 132.2 (2C), 131.45 (d, $^2J$(P,C) = 9.5 Hz, 4C), 128.6 (d, $^3J$(P,C) = 12 Hz, 4C), 44.5, 35.6 (d, $^3J$(P,C) = 5 Hz, 2C), 25.8 (2C), 25.35; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 42.49$; IR (KBr): $\tilde{\nu} = 3057$, 2931, 2853, 1438, 1196, 1114, 996, 751, 726, 698, 570 cm$^{-1}$; MS (ESI-TOF): $m/z$ (%): 316 $[M]^+$ (100), 338 $[M+Na]^+$ (30); elemental analysis calcd (%) for $C_{18}H_{21}OPS$: C 68.33, H 6.69; found C 68.33; H 6.66.

**Diphenylphosphinothioic *S*-benzyl ester (6c)**: Colorless crystals; m.p. 87–88 °C; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.92-7.83$ (m, 4H), 7.54–7.39 (m, 6H), 7.22–7.15 (m, 5H), 4.03 (d, $^3J$(P,H) = 9 Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 136.8$, 133.1 (d, $^1J$(P,C) = 107 Hz, 2C), 132.4 (2C), 131.6 (d, $^2J$(P,C) = 9 Hz, 2C), 129.0 (d, $^3J$(P,C) = 14 Hz, 2C), 128.8 (4C), 127.5, 33.3; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 43.40$; IR (KBr): $\tilde{\nu} = 3058$, 1437, 1192, 1114, 996 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 325 $[M+H]^+$ (70), 342 $[M+NH_4]^+$ (100); elemental analysis calcd (%) for $C_{19}H_{17}OPS$: C, 70.35, H, 5.28; found C, 70.52; H, 5.31.

**Diphenylphosphinothioic *S*-(3-hydroxypropyl) ester (6d)**: Pale yellow oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.92-7.81$ (m, 4H), 7.61–7.43 (m, 6H), 3.79 (t, $^3J$(H,H) = 6.0 Hz, 2H) 2.93 (dt, $^3J$(P,H) = 13 Hz, $^3J$(H,H) = 6.0 Hz, 2H), 1.83 (quint., $J$(H,H) = 6.0 Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 132.9$ (d, $^1J$(P,C) = 108 Hz, 2C), 132.6 (2C), 131.6 (d, $^2J$(P,C) = 6 Hz, 2C), 128.8 (d, $^3J$(P,C) = 14 Hz, 2C), 58.4, 33.1, 25.8; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 46.92$; IR (neat): $\tilde{\nu} = 3383$ (broad), 3058, 2932, 2871, 1436, 1183, 1114, 1065 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 293 $[M+H]^+$ (100), 310 $[M+NH_4]^+$ (30).

**Diphenylphosphinothioic acid *S*-(3-cyanopropyl) ester (6e)**: Pale yellow oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.92-7.80$ (m, 4H), 7.59–7.42 (m, 6H), 2.87 (dt, $^3J$(P,H) = 14.5 Hz, $^3J$(H,H) = 7.0 Hz, 2H), 2.46 (t, $^3J$(H,H) = 7.0 Hz, 2H), 2.01 (quint., $J$(H,H) = 7.0 Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 134.7$ (d, $^1J$(P,C) = 110 Hz, 2C), 132.7 (2C), 131.5 (d, $^2J$(P,C) = 7 Hz, 2C), 128.9 (d, $^3J$(P,C) = 12 Hz, 2C), 118.8 (CN), 28.1, 26.6, 15.95; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 44.00$; IR (neat): $\tilde{\nu} = 3058$, 2929, 2247 (CN), 1589, 1481, 1436, 1196, 1115, 1097 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 302 $[M+H]^+$ (40), 319 $[M+NH_4]^+$ (100).

**Thiophosphoric *S*-cyclohexyl ester *O,O′*-diethyl ester (7b)**: Pale orange oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 4.12$ (m, 4H); 3.21 (q of t, $^3J$(P,H) = $^3J$($H_{ax}$,$H_{ax}$) = 11.5 Hz; $^3J$($H_{ax}$,$H_{eq}$) = 3.5 Hz, 1H), 2.05 (m, 2H), 1.75 (m, 2H), 1.55–1.20 (m, 6H), 1.32 (t, $^3J$(H,H) = 7.0 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 63.45$ (d, $^2J$(P,C) = 5 Hz, 2C), 45.6 (d, $^2J$(P,C) = 5 Hz), 35.35, 35.3, 25.9 (2C), 25.3, (d, $^3J$(P,C) = 6 Hz, 2C); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 28.23$; IR (neat): $\tilde{\nu} = 2984$, 2933, 2856, 1448, 1251, 1019, 968 cm$^{-1}$; MS (ESI-TOF): $m/z$ (%): 252 $[M+H]^+$, 274 $[M+Na]^+$ (100).

**Thiophosphoric acid *S*-benzyl ester *O,O′*-diethyl ester (7c)**: Colorless oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 7.35-7.25$ (m, 5H), 4.09 (m, 4H), 3.99 (d, $^3J$(P,H) = 14.5 Hz, 2H), 1.42 (t, $^3J$(H,H) = 7 Hz, 6H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 138.5$ (d, $^3J$(P,C) = 5 Hz), 129.9 (2C), 129.7 (2C), 128.6, 64.5 (d, $^2J$(P,C) = 7 Hz, 2C), 36.0, 16.95 (d, $^3J$(P,C) = 6 Hz, 2C); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 27.22$; IR (neat): $\tilde{\nu} = 2981$, 2929, 2601, 2495, 2052, 1496, 1476, 1454, 1393, 1256, 1014, 972 cm$^{-1}$; MS (I.C./$NH_3$): $m/z$ (%): 261 $[M+H]^+$, 278 $[M+NH_4]^+$ (100).

**Thiophosphoric acid *O,O′*-diethyl ester *S*-(3-hydroxypropyl) ester (7d)**: Yellow oil, rapidly turning brown upon standing at room temperature; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 4.19$ (m, 4H), 3.77 (t, $^3J$(H,H) = 6.5 Hz, 2H), 3.02 (td, $^3J$(P,H) = 17 Hz, $^3J$(H,H) = 6.5 Hz, 2H), 1.90 (quint. $^3J$(H,H) = 6.5 Hz, 2H), 1.33 (t, $^3J$(H,H) = 7.0 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 64.0$ (2C), 59.3, 33.5, 27.2 (d, $^2J$(P,C) = 5.0 Hz), 16.1 (d, $^3J$(P,C) = 7.5 Hz, 2C); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 27.35$; MS (I.C./$NH_3$): $m/z$ (%): 229 $[M+H]^+$ (70), 246 $[M+NH_4]^+$ (100).

**Thiophosphoric *S*-(3-cyanopropyl) ester *O,O′*-diethyl ester (7e)**: Pale orange oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta = 4.32-4.05$ (m, 4H), 2.93



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(td, $^3J$(P,H) = 16.5 Hz, $^3J$(H,H) = 6.5 Hz, 2H), 2.49 (t, $^3J$(H,H) = 6.5 Hz, 2H), 2.08 (quint, $^3J$(H,H) = 6.5 Hz, 2H), 1.31 (t, $^3J$(H,H) = 7 Hz, 6H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 118.7(CN), 63.95 (d, $^2J$(P,C) = 7.5 Hz, 2C), 29.3, 26.7 (d, $^3J$(P,C) = 5 Hz), 16.1 (d, $^3J$(P,C) = 7.5 Hz, 2C), 15.93; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 27.12; IR (neat): $\tilde{\nu}$ = 2986, 2938, 2248 (CN), 1248, 1016, 972 cm$^{-1}$; MS (ESI-TOF): *m*/*z* (%): 237 $[M]^+$, 259 $[M+Na]^+$.

**Thiophosphoric *O,O′*-dibenzyl ester *S*-cyclohexyl ester (8b)**: Colorless oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta$ = 7.45–7.35 (m, 10H), 5.20–5.05 (ABX system, two dd, $^2J$(H,H) = 8.5 Hz, $^3J$(P,H) = 16.5 Hz, 4H), 3.25 (q of t, $^3J$(P,H) = $^3J$($H_{ax}$,$H_{ax}$) = 10.5 Hz; $^3J$($H_{ax}$,$H_{eq}$) = 3.5 Hz, 1H), 2.05 (m, 2H), 1.72 (m, 2H), 1.57–1.40 (m, 3H), 1.35–1.20 (m, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 131.2 (d, $^2J$(P,C) = 6 Hz, 2C) 128.6 (4C), 128.5 (2C), 128.1 (4C), 68.9 (d, $^2J$(P,C) = 10 Hz, 2C), 45.9, 35.3 (d, $^3J$(P,C) = 6 Hz, 2C), 25.9 (2C), 25.3; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 29.33; IR (neat): $\tilde{\nu}$ = 2932, 2854, 1453, 1252, 992 (broad), 738, 696 cm$^{-1}$; MS (ESI-TOF): *m*/*z* (%): 376 $[M]^{+\cdot}$, 398 $[M+Na]^+$ (100).

**Thiophosphoric *S*-benzyl ester *O,O′*-dibenzyl ester (8c)**: Yellow oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta$ = 7.39 (m, 15H), 5.07 (ABX system, $^3J$(P,H) = 11.5 Hz, 4H), 4.03 (d, $^3J$(P,H) = 14.0 Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 137.3, 135.5 (d, $^3J$(P,C) = 7 Hz, 2C), 129.2 (2C), 128.7 (8C), 128.25 (4C), 127.7, 69.0 (d, $^2J$(P,C) = 7.5 Hz, 2C), 35.1; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 28.43; IR (neat): $\tilde{\nu}$ = 3063, 3032, 1496, 1455, 1378, 1260 (broad), 987 (broad) cm$^{-1}$; MS (I.C./$NH_3$): *m*/*z* (%): 385 $[M+H]^+$ (10), 402 $[M+NH_4]^+$ (100); elemental analysis calcd (%) for $C_{21}H_{21}O_3PS$: C 65.61, H 5.51; found C 65.47, H 5.61.

**Thiophosphoric *O,O′*-dibenzyl ester *S*-(3-hydroxypropyl) ester (8d)**: Flash chromatography was performed with $CH_2Cl_2$/MeOH (8:2) as eluting system. Colorless oil; $^1$H NMR (300.15 MHz, $CD_3OD$): $\delta$ = 7.42–7.25 (m, 10H), 4.92 (AB–X system, $^3J$(P,H) = 15 Hz, $^2J$(H,H) = 3.0 Hz, 4H), 3.62 (t, $^3J$(H,H) = 6.0 Hz, 2H), 2.80 (td, $^3J$(P,H) = 13.5 Hz, $^3J$(H,H) = 6.0 Hz, 2H), 1.81 (quint., $^3J$(H,H) = 6.0 Hz); $^{13}$C NMR (75.4 MHz, $CD_3OD$): $\delta$ = 139.4 (d, $^3J$(P,C) = 10 Hz, 2C), 129.4 (4C), 128.6 (2C), 128.4 (4C), 68.4 (2C), 61.2, 34.75 (d, $^2J$(P,C) = 5 Hz), 27.9; $^{31}$P NMR (121.5 MHz, $CD_3OD$): $\delta$ = 20.35; MS (I.C./$NH_3$): *m*/*z* (%): 353 $[M+H]^+$ (50), 370 $[M+NH_4]^+$ (100).

**10-Cyclohexyl-9-oxa-10-phosphaphenanthrene 10-oxide (9b)**: Colorless oil; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta$ = 7.99 (dt, *J*(H,H) = 8.0, 1.0 Hz, 1H), 7.95–7.88 (m, 3H), 7.68 (tt, *J*(H,H) = 1.0, 8.0 Hz, 1H), 7.49 (dtd, *J*(H,H) = 8.0, 4.0, 1.0 Hz, 1H), 7.38 (tt, *J*(H,H) = 1.0, 8.0 Hz), 7.26 (tt, *J*(H,H) = 1.0, 8.0 Hz, 1H), 7.21 (dd, *J*(H,H) = 1.0, 8.0 Hz, 1H), 3.54 ((q of t, $^3J$(P,H) = $^3J$($H_{ax}$,$H_{ax}$) = 12 Hz, $^3J$($H_{ax}$,$H_{eq}$) = 3 Hz, 1H), 2.13–1.95 (m, 2H), 1.70–1.15 (m, 8H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 149.5 (d, $^2J$(P,C) = 7 Hz), 136.05, (d, $^2J$(P,C) = 7 Hz), 133.7, 130.7, 130.35 (d, $^2J$(P,C) = 10 Hz), 128.6 (d, $^3J$(P,C) = 12 Hz), 125.5 (d, $^1J$(P,C) = 135 Hz), 125.25, 125.0, 123.9 (d, $^3J$(P,C) = 10 Hz), 122.6, 120.5 (d, $^4J$(P,C) = 7 Hz), 45.4, 35.8, 35.2 (d, $^2J$(P,C) = 7 Hz), 26.0, 25.2 (2C); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 38.48; IR (neat): $\tilde{\nu}$ = 2931, 2853, 1607, 1594, 1582, 1475, 1447, 1430, 1235, 1202, 1116, 907 cm$^{-1}$; MS (I.C./$NH_3$): *m*/*z* (%): 331 $[M+H]^+$ (25), 348 $[M+NH_4]^+$ (100); elemental analysis calcd (%) for $C_{18}H_{19}O_2PS$: C 65.44, H 5.80; found C 65.51, H 5.94.

**10-Benzylsulfanyl-9-oxa-10-phosphaphenanthrene 10-oxide (9c)**: White powder; m.p. 75–75.5 °C; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta$ = 7.97 (dt, *J*(H,H) = 7.5, 1.0 Hz, 1H), 7.94–7.87 (m, 3H), 7.68 (tt, *J*(H,H) = 1.0, 7.5 Hz, 1H), 7.48 (dtd, *J*(H,H) = 8.0, 4.0, 1.0 Hz, 1H), 7.33 (tt, *J*(H,H) = 1.0, 7.5 Hz), 7.29–7.22 (m, 6H), 7.01 (dd, *J*(H,H) = 1.0, 8.0 Hz, 1H), 4.18 (t, $^3J$(P,H) = $^2J$(H,H) = 12 Hz, 1H), 4.09 (t, $^3J$(P,H) = $^2J$(H,H) = 12 Hz, 1H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 149.5 (d, $^3J$(P,C) = 10 Hz), 136.9 (d, $^3J$(P,C) = 5 Hz), 136.2, 133.9, 130.7, 130.6 (d, $^2J$(P,C) = 17 Hz), 129.1 (2C), 128.8 (2C), 128.7 (d, $^3J$(P,C) = 9.5 Hz), 127.7, 125.5 (d, $^1J$(P,C) = 134 Hz), 125.2, 125.05, 123.85 (d, $^3J$(P,C) = 9 Hz), 122.2 (d, $^2J$(P,C) = 12 Hz), 120.5 (d, $^4J$(P,C) = 5 Hz), 34.2; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 37.78; IR (KBr): $\tilde{\nu}$ = 3062, 3032, 2979, 1588, 1491, 1471, 1451, 1425, 1264, 1234, 1201, 1112, 902 cm$^{-1}$; MS (I.C./$NH_3$): *m*/*z* (%): 339 $[M+H]^+$ (25), 356 $[M+NH_4]^+$ (100); elemental analysis calcd (%) for $C_{19}H_{15}O_2PS$: C 67.44, H 4.47; found C 67.35, H 4.38.

**4-(10-Oxo-10*H*-9-oxa-10-phosphaphenanthren-10-ylsulfanyl)-butyronitrile (9e)**: White powder; m.p. 173–175 °C; $^1$H NMR (300.15 MHz, $CDCl_3$): $\delta$ = 7.98 (dt, *J*(H,H) = 6.0, 1.0 Hz, 1H), 7.94–7.88 (m, 3H), 7.73 (tt, *J*(H,H) = 1.5, 8.0 Hz, 1H), 7.54 (dtd, *J*(H,H) = 8.0, 4.0, 1.0 Hz, 1H), 7.42 (tt, *J*(H,H) = 1.5, 8.0 Hz), 7.29 (t, *J*(H,H) = 6.0 Hz, 1H), 7.21 (dd, *J*(H,H) = 1.0, 8.0 Hz, 1H), 3.12–2.85 (m, 2H), 2.48 (t, *J*(H,H) = 7.0 Hz, 2H), 2.08 (quint d, $^3J$(H,H) = 7.0 Hz, $^4J$(P,H) = 3.5 Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 149.3 (d, $^2J$(P,C) = 10 Hz), 136.15, 134.2, 131.0, 130.4 (d, $^2J$(P,C) = 12 Hz), 128.8 (d, $^3J$(P,C) = 17 Hz), 125.45 (d, $^1J$(P,C) = 139 Hz), 125.3 (2C), 124.1 (d, $^3J$(P,C) = 10 Hz), 122.5 (d, $^2J$(P,C) = 12 Hz), 120.4 (d, $^4J$(P,C) = 7 Hz), 118.7 (CN), 28.55, 26.90, 16.0; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 37.77; IR (KBr): $\tilde{\nu}$ = 2940, 2246 (CN), 1704, 1475, 1429, 1237, 1119 cm$^{-1}$; MS (I.C./$NH_3$): *m*/*z* (%): 333 $[M+NH_4]^+$ (100); elemental analysis calcd (%) for $C_{16}H_{14}NO_2PS$: C 60.94, H 4.48; found C 59.21; H 4.44.

**Phenylphosphonothioic *S*-(2-diisopropylaminoethyl) ester *O*-ethyl ester PhX (11)**: Phosphinate **4a** (720 μL, 4.5 mmol) and thiocyanate **3a** (838 mg, 4.5 mmol) were stirred together at room temperature under a gentle nitrogen flow for 10 days. Once $^{31}$P NMR analysis of the crude mixture showed completion of the reaction, two successive silica gel chromatographic separations ($CH_2Cl_2$/MeOH 90:10 and then 95:5) were undertaken. Extra purification was achieved by semipreparative HPLC with a Zorbax SB-CN column, a mixture of hexane/methyl *tert*-butyl ether (60:40) as mobile phase, and UV detection at 214 nm, yielding phosphonothioate **11** (500 mg) as a colorless oil. Analytical HPLC analysis with the same elution conditions and detection method showed that **11** thus purified was >95% pure. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.91 (m, 2H), 7.56–7.43 (m, 3H), 4.29–4.20 (m, 2H), 2.91 (hept, $^3J$(H,H) = 7 Hz, 2H), 2.73–2.63 (m, 2H) 2.58–2.52 (m, 2H), 1.39 (t, $^3J$(H,H) = 7 Hz, 3H), 0.92 (d, $^3J$(H,H) = 7 Hz, 12H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 133.3 (d, $^1J$(P,C) = 126 Hz), 132.5, 131.3 (d, $^2J$(P,C) = 10 Hz, 2C), 128.5 (d, $^3J$(P,C) = 14 Hz, 2C), 62.1 (d, $^2J$(P,C) = 6 Hz), 48.9, 46.3 (d, $^3J$(P,C) = 4 Hz), 30.1, 20.9 (4C), 16.4 (d, $^3J$(P,C) = 4 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 46.0; IR (neat): $\tilde{\nu}$ = 3059, 2966, 2930, 1464, 1439, 1363, 1234, 1119, 1024, 952 cm$^{-1}$; MS (I.C./$NH_3$): *m*/*z* (%): 330 $[M+H]^+$.

**Phenylphosphonothioic *S*-(2-diisopropylaminoethyl) ester (12)**: Phosphinic acid **10** (337 mg, 2.37 mmol) and thiocyanate **3a** (423 mg, 2.37 mmol) were dissolved in THF (4 mL) and stirred together at room temperature under a gentle nitrogen flow for 10 days. $^{31}$P NMR analysis of the crude mixture showed a mixture (ca. 50:50) of phosphonothioic acid **12** and remaining starting material **10**. Silica gel chromatography ($CH_2Cl_2$/MeOH 80:20) yielded pure phosphonothioic acid **12** (192 mg, 56%) as a white powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.92–7.82 (m, 2H), 7.49–7.41 (m, 3H), 3.72 (hept, $^3J$(H,H) = 6.5 Hz, 2H), 3.35 (t, $^3J$(H,H) = 6 Hz, 2H), 2.84 (dt, $^3J$(H,H) = 6 Hz, $^3J$(P,H) = 15 Hz, 2H), 1.42 (d, $^3J$(H,H) = 6.5 Hz, 12H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 139.7 (d, $^1J$(P,C) = 146 Hz), 132.2, 132.0 (d, $^2J$(P,C) = 10 Hz, 2C), 129.2 (d, $^3J$(P,C) = 12 Hz, 2C), 56.0 (2C), 50.6, 27.3 , 19.2, 17.6 (4C); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 31.3; MS (I.C./$NH_3$): *m*/*z* (%): 302 $[M+H]^+$.

**Phenylphosphonothioic O-ethyl ester *S*-(2-(isopropyl-propionylamino)-ethyl) ester (13)**: Pale yellow oil; $^1$H and $^{31}$P NMR analysis revealed an equilibrium between two rotamers at room temperature, with heating at 60 °C resulting in the merging of the two signals. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.88–7.83 (m, 2H), 7.49–7.45 (m, 3H), 4.24 (m, 2H), 3.95 (hept, $^3J$(H,H) = 6.5 Hz, 1H), 3.33 (m, 2H), 2.79–2.71 (m, 2H), 2.29 (q, $^3J$(H,H) = 7.0 Hz, 2H), 1.38 (t, $^3J$(H,H) = 7 Hz, 3H; first rotamer), 1.37 (t, $^3J$(H,H) = 7 Hz, 3H; second rotamer), 1.13 (d, $^3J$(H,H) = 6.5 Hz, 6H), 1.08 (t, $^3J$(H,H) = 7 Hz, 3H; first rotamer), 1.07 (t, $^3J$(H,H) = 7 Hz, 3H; second rotamer); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 173.5, 134.0 (d, $^1J$(P,C) = 150 Hz), 132.6, 131.2 (d, $^2J$(P,C) = 11 Hz, 2C), 128.6 (d, $^2J$(P,C) = 14 Hz, 2C), 62.4 (d, $^2J$(P,C) = 6 Hz), 48.1, 42.0, 27.9, 26.8, 21.1 (2C), 16.4 (d, $^3J$(P,C) = 5.5 Hz), 9.5; $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 45.4 (first rotamer), 44.5 (second rotamer); IR (neat): $\tilde{\nu}$ = 2977, 1640, 1420, 1291, 1225, 1119, 1070, 1022, 953 cm$^{-1}$; MS (I.C./$NH_3$): *m*/*z* (%): 344 $[M+H]^+$.

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